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Effect of Carbetocin on Blood Loss after Cesarean Section or Vaginal Delivery

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Abstract

Background: Postpartum hemorrhage (PPH) is a significant cause of maternal morbidity and mortality. This study aimed to evaluate and compare between carbetocin & oxytocin for post-partum haemorrhage prophylaxis among high-risk women giving birth through Vaginal Delivery and Caesarean Section. **Methods:** total of 200 singleton pregnant women with at least one risk factor for atonic PPH were included in the study. They were randomly assigned to two groups: Group A received carbetocin (n=100) and Group B received oxytocin (n=100). Clinical assessments, including blood pressure monitoring, blood loss measurement, and changes in hemoglobin concentrations, were conducted. Maternal demographics, risk factors, and outcomes such as PPH, need for additional uterotonics, and blood transfusion were analyzed. **Results:** Postpartum, both groups experienced increased pulse and blood pressure, with the oxytocin group showing considerably higher systolic and diastolic blood pressure (P-value < 0.001). Hemoglobin and hematocrit levels considerably decreased postpartum, with the oxytocin group exhibiting greater decreases (P-value < 0.001). Estimated blood loss, PPH incidence, and the need for additional uterotonics and blood transfusion were considerably lower in the carbetocin group (P-value < 0.001). Uterine tone was considerably better in the carbetocin group compared to the oxytocin group (P-value < 0.001). **Conclusions:** Carbetocin demonstrated superior efficacy in reducing blood loss and preventing PPH compared to oxytocin among high-risk women undergoing vaginal delivery and cesarean section.

Keywords: Carbetocin; Oxytocin, Postpartum Hemorrhage, Vaginal Delivery, Cesarean Section.

1. Introduction

Postpartum hemorrhage (PPH) is a significant obstetric complication characterized by excessive bleeding following childbirth, posing a major threat to maternal health and well-being. It remains one of the leading causes of maternal morbidity and mortality worldwide, particularly in high-risk populations. Prompt and effective management of PPH is essential to prevent adverse outcomes [1].

Current guidelines recommend the use of oxytocin as the standard prophylactic agent for preventing PPH. Oxytocin, a uterotonic medication, is commonly administered during the third stage of labor to reduce the risk of excessive bleeding. It stimulates uterine contractions, leading to improved uterine tone and decreased blood loss. Despite its widespread use, there is room for exploring alternative prophylactic agents that could potentially enhance the effectiveness of PPH prevention [2, 3].

Carbetocin, a long-acting synthetic analogue of oxytocin, has emerged as a promising alternative for PPH prophylaxis. It shares similar pharmacological properties with oxytocin but exhibits an extended half-life, allowing for a sustained effect on uterine contraction. Carbetocin has demonstrated efficacy in reducing blood loss and the need for additional uterotonics in previous studies focused on elective and emergency CS [4, 5].

Given the importance of PPH prevention and the potential advantages of carbetocin, it is essential to evaluate and compare the effectiveness of carbetocin and oxytocin as prophylactic agents among high-risk women undergoing vaginal delivery and CS [6, 7].

Therefore, this study aimed to evaluate and compare between carbetocin & oxytocin for post-partum haemorrhage prophylaxis among high-risk women giving birth through Vaginal Delivery and Caesarean Section.

2. Methods

This prospective randomized-controlled blinded clinical trial was conducted to evaluate and compare the effect of carbetocin and oxytocin on PPH prophylaxis among high-risk women undergoing vaginal delivery and CS. The study was at the obstetrics and gynecology department of Benha University Hospital from April to October 2022.

Informed written consent was obtained from all patients, and their privacy and data confidentiality were strictly protected. The study adhered to the principles outlined in The Declaration of Helsinki and the guidelines of good clinical practice.

Inclusion criteria were singleton pregnant women who underwent elective or emergency

lower segment CS or vaginal delivery and had a gestational age of at least 34 weeks, induction or augmentation of labor exceeding 4 hours,participants needed to have at least one risk factor for atonic PPH, polyhydramnios, twin pregnancy, a prolonged active phase of labor exceeding 12 hours, precipitated labor, grand multiparity (parity > 4), or the presence of uterine leiomyoma.

Exclusion criteria were patients with underlying medical conditions including cardiovascular diseases, anemia, bleeding disorders, thrombocytopenia, liver and renal diseases, asthma, epilepsy, and migraine, obstetric complications, history of carbetocin allergy, and the need for emergency cesarean delivery and patients with non-atonic PPH.

The study included 200 patients who were randomly assigned to two groups: Group A (n=100) received 100 µg of carbetocin (Bleedaceas®; IBSA, Lugano, Switzerland), and Group B (n=100) received 10 IU of oxytocin (Syntocinon®; Alliance, Chippenham, UK).

Clinical assessments were conducted for all included patients, which involved obtaining detailed medical history, including demographic data, comorbidities, presenting symptoms, history of PPH in previous pregnancies, and the need for blood transfusion. General examinations were performed, including monitoring of blood pressure at different time points, assessment of signs of shock, and measurement of blood loss immediately after labor. The volume of lost blood was estimated using a standardized method of weighing soaked dressings and calculating the volume based on the assumption that weight is due only to blood and not environmental water or debris. Changes in hemoglobin concentrations before and 24 hours postoperative were also measured. Possible complications such as nausea, tachycardia, vomiting, flushing, dizziness, shivering, headache, dyspnea, palpitation, metallic taste, and itching were recorded.

Local obstetric examinations were conducted to evaluate uterine tone by palpation and assess risk factors for traumatic PPH, including episiotomy and lacerations. Laboratory testing, including complete blood count (CBC), urine output, coagulation profile, liver function tests, and renal function tests, was performed. Obstetric ultrasound was conducted on admission to assess fetal well-being, determine gestational age, identify any obstetric problems such as placenta previa or multiple gestation, and examine the placenta and amniotic fluid.

Statistical analysis:

Statistical analysis was performed using version 26 of IBM SPSS Statistics (IBM Inc., Armonk, NY, USA). Using the Shapiro-Wilks test and histograms, the normality of data distribution was analyzed. Using the unpaired Student's t-test, quantitative parametric data were reported as mean and standard deviation (SD) and evaluated as such. Using the Mann-Whitney U test, non-parametric quantitative data were presented as median and interquartile range (IQR) and evaluated as median and IQR. When applicable, qualitative data were presented as frequency and percentage (percent) and evaluated using the Chi-square test or Fisher's exact test. A two-tailed P value of less than 0.05 was regarded as statistically significant.

3. Results

Demographic characteristics, risk factors were insignificantly different between the studied groups. In Carbetocin and Oxytocin groups, pulse was considerably increased postpartum than before drug administration (P value <0.001 and 0.006 respectively). SBP before drug administration was considerably increased in Oxytocin group than Carbetocin group (P value <0.001). In Oxytocin groups, SBP was considerably increased postpartum than before drug administration (P value <0.001). DBP was considerably increased in Oxytocin group than Carbetocin group (P value =0.001). In Carbetocin and Oxytocin groups, DBP was considerably increased postpartum than before drug administration (P value 0.044 and <0.001 respectively). **Table 1**

Table (1) Demographic characteristics, risk factors and vital signs of the studied groups

		Carbetocin group (n=100)	Oxytocin group (n=100)	P value
Maternal age (years)	Mean ± SD	33.08 ± 3.24	32.86 ± 3.09	0.624
	Range	28 - 38	28 - 38	
BMI (kg/m^2)	Mean ± SD	28.06 ± 2.52	27.79 ± 2.43	0.436
	Range	23.72 - 32.19	23.62 - 32.2	
GA (weeks)	Mean ± SD	36.42 ± 2.25	36.39 ± 1.88	0.919
	Range	33 - 40	34 – 39	

Gravidity	Median IQR	4 3 – 5	4 3 - 5	0.401
Parity	Median IQR	2 2 – 3	3 2 - 4	0.123
Mode of delivery	Vaginal delivery CS	58 (58%) 42 (42%)	50 (50%) 50 (50%)	0.256
Risk factors				
Previous PPH		27 (27%)	25 (25%)	0.747
Leiomyoma		4 (4%)	11 (11%)	0.060
Polyhydramnios		13 (13%)	9 (9%)	0.366
Prolonged induction		11 (11%)	14 (14%)	0.521
Prolonged tocolytic		8 (8%)	11 (11%)	0.469
Multiparity		30 (30%)	27 (27%)	0.638
Augmentation		9 (9%)	6 (6%)	0.421
Vital signs				
Pulse before drug administration (beats/min)	Mean ± SD	86.89 ± 4.51	87.43 ± 4.51	0.398
	Range	80 - 95	80 - 97	
Pulse postpartum^ (beats/min)	Mean ± SD	89.4 ± 4.27	89.32 ± 5.04	0.904
	Range	81 - 97	82 - 99	
P value		**<0.001***	**0.006***	
SBP before drug administration (mmHg)	Mean ± SD	110.94 ± 7.13	109.5 ± 7.19	0.156
	Range	98 - 122	98 - 122	
SBP postpartum^ (mmHg)	Mean ± SD	112.22 ± 6.62	117.56 ± 10.28	**<0.001***
	Range	100 - 122	98 - 134	
P value		0.190	**<0.001***	
DBP before drug administration (mmHg)	Mean ± SD	74.68 ± 4.78	74.76 ± 4.79	0.906
	Range	66 - 83	67 - 85	
DBP postpartum^ (mmHg)	Mean ± SD	76.06 ± 4.87	79.93 ± 10.83	**0.001***
	Range	68 - 84	60 – 100	
P value		**0.044***	**<0.001***	

Hb before drug administration was considerably decreased in Oxytocin group than Carbetocin group (P value =0.002). In Oxytocin groups, Hb was considerably decreased postpartum than before drug administration (P value <0.001). Hb drop was considerably increased in Oxytocin group than Carbetocin group (P value <0.001). HCT before drug administration was considerably decreased in Oxytocin group than Carbetocin group (P value <0.001). In Carbetocin and Oxytocin groups, HCT was considerably decreased postpartum than before drug administration (P value <0.001). HCT drop was considerably increased in Oxytocin group than Carbetocin group (P value <0.001). **Table**

Table (2) Hb and HCT of the studied groups

		Carbetocin group (n=100)	Oxytocin group (n=100)	P value
Hb before drug administration (g/dl)	**Mean ± SD**	10.52 ± 0.73	10.7 ± 0.6	0.068
	Range	9.2 - 11.9	9.3 - 11.7	
Hb postpartum (g/dl)	**Mean ± SD**	10.37 ± 0.65	10.05 ± 0.77	**0.002***
	Range	8.6 - 11.3	8.2 - 11	
P value		0.128	**<0.001***	
Hb drop (g/dl)	**Mean ± SD**	0.15 ± 1.07	0.65 ± 0.9	**<0.001***
	Range	-2.1 - 3.3	-1.2 - 2.8	
HCT before drug	**Mean ±**	32.15 ± 2.39	32.66 ± 1.96	0.102

administration (g/dl)	**SD**			
	Range	28.2 - 36	29.2 - 35.7	
HCT postpartum (g/dl)	**Mean ± SD**	29.63 ± 2.27	28.69 ± 1.66	**<0.001***
	Range	26 - 33	26.8 - 35	
P value		**<0.001***	**<0.001***	
HCT drop (g/dl)	**Mean ± SD**	2.52 ± 2.17	3.97 ± 2.26	**<0.001***
	Range	-3.2 - 8.3	0.5 - 7.9	

Hb: hemoglobin, HCT: hematocrit, *: significant as P value ≤ 0.05

Estimated blood loss, need for additional uterotonics, PPH, and blood transfusion were considerably increased in Oxytocin group than Carbetocin group (P value < 0.001, 0.046, 0.027 and 0.033 respectively). Soft uterine tone was considerably increased in Oxytocin group than Carbetocin group (P value = 0.005). **Table 3**

Table (3) Outcomes of the studied groups

		Carbetocin group (n=100)	Oxytocin group (n=100)	P value
Estimated blood loss (ml)	**Mean ± SD**	826.8 ± 105.8	1159.5 ± 195	**<0.001***
	Range	453 - 1100	753 - 1405	
PPH		7 (7%)	16 (16%)	**0.046***
Need for additional uterotonics		9 (9%)	20 (20%)	**0.027***
Blood transfusion		2 (2%)	10 (10%)	**0.033***
Uterine tone	**Soft**	6 (6%)	19 (19%)	**0.005***
	Firm	94 (94%)	81 (81%)	
Hysterectomy		0 (0%)	0 (0%)	-

PPH: postpartum hemorrhage, *: significant as P value ≤ 0.05

Adverse effects (nausea, vomiting, headache, dyspnea, and itching) were insignificantly different between the studied groups. **Fig. (1)**

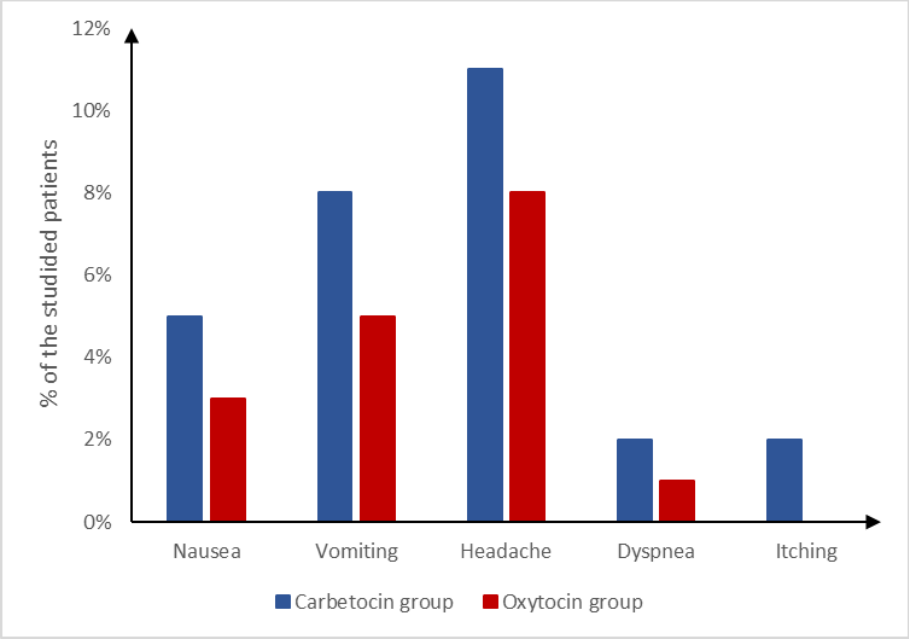

Fig. (1) Adverse effects of the studied groups

Regarding Carbetocin group, there was a significant relationship between PPH and estimated blood loss, need for additional uterotonics and blood transfusion (P value <0.001, <0.001 and 0.004 respectively) as they were increased in patients who developed PPH while there was an insignificant relationship between PPH and mode of delivery. **Table 4**

Table (4) Relationship between PPH and different parameters of Carbetocin group (n=100)

		PPH		P value
		Yes (n=7)	**No (n=93)**	
Mode of delivery	**Vaginal delivery**	4 (57.1%)	54 (58.1%)	1.000
	CS	3 (42.9%)	39 (41.9%)	
Estimated blood loss (ml)		1033.6 ± 53.37	745.8 ± 44.5	**<0.001***
Need for additional uterotonics		4 (57.1%)	5 (5.4%)	**<0.001***
Blood transfusion		2 (28.6%)	0 (0%)	**0.004***

PPH: postpartum hemorrhage, CS: cesarean section, *: significant as P value ≤ 0.05

Regarding Oxytocin group, there was a significant relationship between PPH and need for additional uterotonics, estimated blood loss, and blood transfusion (P value 0.044, <0.001 and <0.001 respectively) as they were increased in patients who developed PPH while there was an insignificant relationship between PPH and mode of delivery. **Table 5**

Table(5) Relationship between PPH and different parameters of Oxytocin group (n=100)

		PPH		P value
		Yes (n=16)	**No (n=84)**	
Mode of delivery	**Vaginal delivery**	6 (37.5%)	44 (52.4%)	0.275
	CS	10 (62.5%)	40 (47.6%)	
Estimated blood loss (ml)		1319.3 ± 98.4	948.7 ± 77.2	**<0.001***
Need for additional uterotonics		9 (56.3%)	11 (13.1%)	**<0.001***
Blood transfusion		8 (50%)	2 (2.4%)	**<0.001***

PPH: postpartum hemorrhage, CS: cesarean section, *: significant as P value ≤ 0.05

Previous PPH and prolonged induction were significant predictors for PPH (OR =28.1, P value <0.001, 95% CI 4.65 – 169.81 for previous PPH and OR =52.7, P value <0.001, 95% CI 11.12 – 249.86 for prolonged induction). Leiomyoma, polyhydramnios, prolonged tocolytic, multiparity, and augmentation were insignificant predictors for PPH. **Table 6**

Table (6) Logistic regression for risk factors in prediction of PPH of the studied patients (n=200)

	Multiple regression		
	OR	**P value**	**95% CI**
Previous PPH	28.1	**<0.001***	4.65 – 169.81
Leiomyoma	0.37	0.561	0.01 – 10.31
Polyhydramnios	0.33	0.481	0.01 – 7.32
Prolonged induction	52.7	**<0.001***	11.12 – 249.86
Prolonged tocolytic	1.88	0.572	0.21 – 16.65
Multiparity	0.72	0.719	0.12 – 4.35
Augmentation	0.78	0.870	0.04 – 16.55

PPH: postpartum hemorrhage, OR: odds ratio, CI: confidence interval, *: significant as P value ≤ 0.05.

4. Discussion

In our study, the postpartum pulse in the Carbetocin and Oxytocin groups was considerably greater than before drug administration, but there was no significant difference across groups. Contrary to our findings, Amornpetchakul et al. discovered that the postpartum pulse rate was considerably lower in the carbetocin group than in the oxytocin group [8]. Additionally, Seow et al. found that the pulse rate in the carbetocin group was considerably higher than in the oxytocin group [9].

In spite of a higher incidence of tachycardia in the carbetocin group compared to the oxytocin group, the tachycardia decreased 60 minutes after injection without treatment. However, it may complicate the monitoring of women with bleeding and lead to a missed diagnosis of PPH due to the hemodynamic instability generated by a rapid heart rate **[10]**.

Regarding SBP and DBP in the present work, a research indicated a substantial drop in SBP in the Oxytocin and Carbetocin groups, but no significant difference across groups. [11]. Our findings are against, some authors found that the DBP postpartum was considerably higher in the carbetocin group than that in the oxytocin group ($p < 0.05$) [8].

A study discovered variations in the hemodynamic condition of carbetocin, oxytocin, and placebo-treated patients following cesarean birth. These findings are

complementary to our own. The researchers discovered comparable hypotensive effects across carbetocin and oxytocin injections, with the hypotensive effects appearing less than 2.5 minutes after delivery with no following hemodynamic instability and moderate side effects [11].

In accordance with our findings, Amornpetchakul et al. found that the 24-hour postpartum hemoglobin levels in the carbetocin group were considerably greater than those in the oxytocin group compared to the predelivery period ($p < 0.01$) [8]. In addition, Seow et al. showed that the Hb levels in the carbetocin and oxytocin groups were comparable before and 24 hours after drug delivery. The decline in Hb levels was similar between groups **[9]**. In contrast, Rosseland et al. discovered that the decrease in Hb level postpartum was not substantially different between the Oxytocin and Carbetocin groups [11].

In the current study, HCT was not substantially different between groups prior to medication administration, however it was considerably lower in the Oxytocin group than the Carbetocin group postoperatively. In the Carbetocin and Oxytocin groups, HCT was considerably reduced postpartum compared to prior drug administration, with the Oxytocin group seeing a greater reduction. Conforming to our findings, Amornpetchakul et al. demonstrated that the 24-h postpartum levels of HCT were substantially greater in the carbetocin group than in the oxytocin group compared to the predelivery period ($p < 0.01$) [8].

In our study, the Oxytocin group had considerably higher estimated blood loss, PPH, need for extra uterotonics, and blood transfusions than the Carbetocin group. In keeping with the findings of Amornpetchakul et al., the carbetocin group experienced reduced postpartum blood loss (P-value < 0.01), a lower incidence of atonic PPH (P-value < 0.01), and less need of extra uterotonic medications (P-value < 0.01) than the oxytocin group [8].

Similar results were discovered by Seow et al. ; the mean quantity of estimated blood loss during surgery was less in the carbetocin group than in the control group, but the difference was not statistically significant (P = 0.06) [9].

In addition, Maged et al. evaluated the efficacy of 100 mcg of intramuscular carbetocin to that of 5 U of intramuscular oxytocin in preventing PPH in 200 term pregnant women with at least two PPH risk factors. Carbetocin was better to oxytocin in terms of postpartum blood loss, the need for extra uterotonic medicines, the requirement for uterine massage, and the change in hemoglobin level, although the hemodynamic effects and safety of the two agents were comparable [12].

Jin et al. concluded in a meta-analysis that the use of carbetocin after vaginal birth reduced the risk of adverse effects, but there was no statistical significance for postpartum hemorrhage, major postpartum hemorrhage, or the need for further uterotonic medicines [10].

In contrary, **Jin et al.** found that there was no significant difference between carbetocin and oxytocin in blood loss ≥500ml or ≥1000ml in women undergoing vaginal delivery **[6]**.

In our study, Oxytocin considerably raised soft uterine tone compared to Carbebecin. In our study, there were no significant differences in side effects (nausea, vomiting, headache, dyspnea, and itching) across the groups. In accordance with our findings, Jin et al. discovered no statistically significant difference between Carbetocin and oxytocin in terms of deleterious effects **[6]**.

In their investigation on adverse effects, Amornpetchakul et al. found no significant differences between the groups. No patient in either the Carbetocin or oxytocin groups required a blood transfusion or had peripartum hysterectomy due to severe bleeding (EBL > 1000 mL) [8]. According to a research, the Carbetocin and oxytocin groups exhibited no notable adverse effects or problems. Due to the intense contraction of the uterus, the most common adverse effects of carbetocin include abdominal discomfort, dizziness, and nausea **[9]**. Patients in the oxytocin group and carbetocin group reported one or more adverse effects after intervention, with more side effects and a higher degree of pain in the oxytocin group, although the differences were not statistically significant [11].

In our study, there was a significant association between PPH and anticipated blood loss, the need for extra uterotonics, and the requirement for blood transfusion in the Oxytocin group, although there was no significant relationship between PPH and method of delivery. In contrast to our findings, earlier research has indicated that manner of delivery (CS) is a significant contributor in the development of PPH [13, 14].

Previous PPH and prolonged induction were significant predictors of PPH in our research, but leiomyoma, polyhydramnios, extended tocolytic, multiparity, and augmentation were not. In this context, a research discovered that difficulties during

labor, past postpartum hemorrhage, and instrumental delivery were predictors of postpartum hemorrhage. [15]. In addition, according to a research, prior cesarean delivery, extended labor, oxytocin augmentation, and emergency cesarean delivery are the biggest predictors of substantial blood loss in women with PPH [16].

5. Conclusion

Carbetocin demonstrated superior effectiveness in reducing blood loss and preventing PPH compared to oxytocin among high-risk women undergoing vaginal delivery and CS. These findings support the potential of carbetocin as a prophylactic agent for PPH in this population, emphasizing its role in improving maternal outcomes.

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